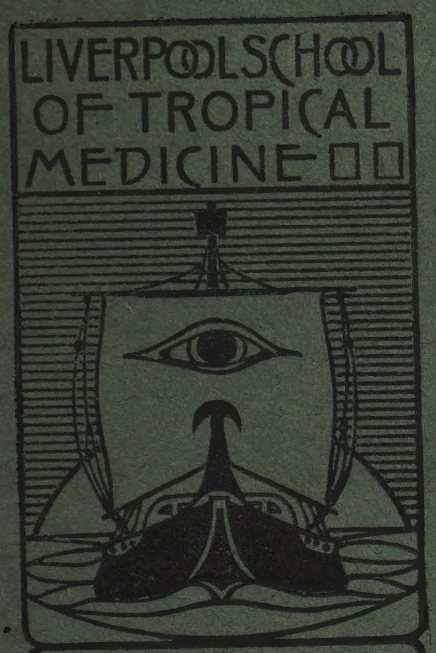

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Edited by
RONALD ROSS
in collaboration
with
J. W. W. STEPHENS
R. NEWSTEAD
J. L. TODD
H. W. THOMAS
ANTON BREINL
SIR RUBERT BOYCE

MY EXPERIENCE OF TRYPANOSOMIASIS IN EUROPEANS AND ITS TREATMENT BY ATOXYL AND OTHER DRUGS

SIR PATRICK MANSON, K.C.M.G., F.R.S.

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MY EXPERIENCE OF TRYPANOSOMIASIS IN EUROPEANS AND ITS TREATMENT BY ATOXYL AND OTHER DRUGS

BY

SIR PATRICK MANSON, K.C.M.G., F.R.S., &c.

(*Received January 23rd, 1908*)

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In view of the recently recorded experiences of Campenhout, Broden, Kopke, Koch and others in the treatment of human trypanosomiasis, especially in negroes, by atoxyl, it may not be inopportune if I gave some account of my experience of this disease in Europeans, and of atoxyl and other drugs in its treatment.

My experience of trypanosomiasis in man extends to seventeen cases—seven negroes, ten whites. The negroes, who had been brought to Europe for purposes of clinical study, and because they had already entered on the terminal phase—sleeping sickness—of the infection, all died. They did not have the benefit of Thomas's important discovery of the therapeutic value of atoxyl. I shall not allude to them further.

Of the ten whites, three of the cases have been recorded already by myself and others. For the sake of completeness I shall briefly mention here these three cases, along with the seven unrecorded cases, giving them along with the latter in the order in which they came under my observation, but referring the reader to the medical journals for details.

I.—Mrs. H. M. was first seen by me on July 17th, 1901. She was then 40 years of age, and had resided on the Congo for two periods of two years and one year respectively. During the latter period she had suffered much from fever. Being pregnant at the time she came home, arriving in England in April, 1901. She had fever all the way home. A week after her arrival her child was born, and from that time till the date of her visit to me she had attacks of fever lasting for three days at a time and occurring at intervals of seven days with considerable regularity. She also suffered with pains in her

hands, ankles and knees, for which she took sodium salicylate with some relief. She informed me that the attacks of fever were preceded and accompanied by a circinate erythematous eruption on her face, limbs and trunk, and that this tended to subside with the subsidence of the fever. She was anaemic and her skin showed traces of the erythema she referred to. The spleen and liver were not palpably enlarged.

As the trypanosoma had not been discovered at that time I regarded the case as one of malaria, and prescribed a systematic course of quinine.

I saw this lady again on April 9th, 1902. She told me she had improved, notwithstanding the fatigue consequent on the illness of her baby which had died on December 19th, 1901 (? trypanosomiasis). Three weeks before her visit to me she had caught a chill and the fever, which had been in abeyance for a long time, had returned. During this period of three weeks she had had three attacks. Nevertheless, as compared with her condition in July, 1901, she had put on flesh and no longer appeared anaemic. She informed me that the patches of erythema still showed themselves at times, but were less pronounced than formerly.

I did not see this patient again at this time, but learned that she had an attack of irido-cyclitis and that subsequently she returned to the Congo.

In the autumn of 1902, after having learned from Dutton's case and from Case No. 3 (to be presently alluded to) that irregular fever along with erythema multiforme were in a patient from tropical Africa probably symptomatic of trypanosomiasis, I wrote to her husband on the Congo requesting that an examination of this lady's blood be made for trypanosomes. Before receiving a reply to my letter I heard from Dr. Broden that he had examined her blood and had found the parasite.

Dr. Broden put her on arsenic (Fowler's solution). The case did well. Fever and trypanosomes disappeared. When I saw her during a subsequent visit to England in 1906-7, by way of encouraging them, I showed this lady to two trypanosomiasis patients I had at the time under treatment as an example of recovery from the disease. She was stout and healthy looking, and was free from all symptoms of the infection. I hear she is still in excellent health.

This patient must have received her infection some time during 1900. The conclusions that she has overcome the infection and that trypanosomiasis in man is not necessarily fatal are, it seems to me, justifiable.

Dr. Broden has published his notes of this case.

II.—H. K. This was Forde's original case in which *Trypanosoma gambiense* was first definitely recognised (and for the first time in human pathology) by Dutton. It has been fully described by Dutton in the publications of the Liverpool School of Tropical Medicine, and elsewhere by Forde. I mention it here as it constituted my first conscious experience of trypanosomiasis in man. I saw the case in August, 1902, and had the clinical points of the disease demonstrated to me by Dutton. It was from what I saw on that occasion that I was enabled to recognise clinically the disease in the next case. The medicinal treatment consisted principally in the administration of arsenic, quinine and urotropin. The patient died the following January, about one year and eight months after the presumed date of infection.

III.—Mrs. S. was seen by me for the first time in October, 1902. She presented the usual clinical picture of trypanosomiasis, and the parasite was found in her blood. The case has already been fully recorded in the British Medical Journal of May 30th and December 6th, 1903, and elsewhere. I may mention here that the first indication of the disease occurred in August, 1901, supervening, apparently, on an insect bite on the leg. The patient died of sleeping sickness on November 26th, 1903, two years and three months after infection. The treatment included arsenic, quinine, methylene blue, and many other drugs, but not atoxyl.

IV.—W. Z., an engineer on one of the lake steamers in Uganda, came under my observation on October 9th, 1905. His story was that early in the year he broke his leg; that on this account and because he suffered from fever he had been in hospital in Uganda for a considerable time; and that trypanosomes having been found in his blood he was invalided on July 26th. On arrival he went to his home in Scotland, where, with the exception of two days' fever, he kept well and put on flesh. He stated, however, that he had suffered from dull pains in his legs and that once he had a swelling in his left foot.

When I saw him, there was a well-marked circinate erythema on his chest, and the cervical and inguinal lymphatic glands were enlarged. On examination of the blood trypanosomes were found. His pulse was rapid—108—his spleen palpable, knee jerks exaggerated, slight right ankle clonus. He complained that he felt weak, and also of subjective symptoms of numbness in the legs. Otherwise he appeared to be well. Blood count 4,000,000. He was sent to hospital.

During his stay there he had a malarial attack and benign tertian parasites were found in his blood. Quinine quickly got rid of this infection. He also developed a specific periostitis which yielded to potassium iodide.

From October 18th, 1905, to January 25th, 1906, he was treated by trypanroth and, later, by trypanroth and arsenious acid, the latter hypodermically. The erythema persisted, however, or, if it faded for a time, would again return. Occasionally the erythematous spots gave one the impression that they were slightly oedematous. Trypanosomes were also occasionally found in the blood, but gland puncture, which was twice practised, was negative. The temperature, except during the malarial attack, remained normal throughout.

The skin and urine became deeply stained by the trypanroth. On January 26th, albumin having appeared in the urine, the trypanroth and arsenious acid were stopped. On February 5th treatment by atoxyl injections was commenced. Beginning with one grain twice a week it was gradually raised to four grains twice a week, at which dose it was continued till the spring of 1907.

Very soon after commencing the atoxyl he became conscious of an improvement in his general health. The erythema no longer showed itself on the trunk, and for over six weeks, notwithstanding frequent and prolonged search, trypanosomes could not be found in his blood. He now insisted on leaving hospital, promising to continue treatment and to report from time to time.

He returned to his home, where he kept in perfect health and gained weight. Wishing to get reinstated in his former appointment in Uganda, he came to London during the autumn of 1906. His blood was again carefully examined for trypanosomes, but none were found. However, a monkey injected (25th August) with his blood developed trypanosomiasis and died.

Once more he returned to Scotland and continued the injections, his health keeping satisfactory in every respect. Early in 1907 he again came up to London. Again his blood was carefully examined with negative result. A monkey injected with the blood failed to develop trypanosomiasis. It was not considered prudent to allow him to return to Uganda, but he was encouraged to seek employment elsewhere, and when an appointment offered in the West Indies he left England in the early spring of 1907. On the voyage out he was shipwrecked, and during eleven days suffered great hardships, wandering about the mangrove swamps at the mouth of the Magdalena river. Nevertheless he kept in perfect health, and when I saw him on his return on 19th April, 1907, he appeared healthy and robust, without trypanosomes in his blood and with no sign of trypanosomiasis about him. As he had lost his syringe and atoxyl when shipwrecked, he had had no injections for many weeks.

Subsequently he again set out for the West Indies, and when last heard of was still in perfect health.

V.—J. M., a botanist and agricultural expert, was in British Central Africa from June, 1897, to September, 1899. I examined and passed him for service in Uganda in March, 1901. He was then 30 years of age and in good health.

He arrived in Uganda on June 17th, 1901. He informed me that before crossing the lake he had several small fevers (probably malarial) at Kusumu. He also informed me that a fortnight after his arrival in Etebbe he was bitten by 'something' in front of his left ankle; the part swelled and he had fever about the same time. With this exception he kept well for a year. About June, 1902, he began to ail—languor, loss of appetite. At Christmas of that year, and on and off till March of 1903, he had several heavy fevers, accompanied by cerebral symptoms. He became melancholic, had delusions of persecution, and at one time was suicidal. Trypanosomes were found in his blood and he was invalided home.

I saw him on August 1st, 1903. He had no fever then, and looked fairly healthy, but his manner was strange and there were definite trypanosoma erythema patches on his trunk and I found trypanosomes in his blood.

I saw him subsequently from time to time. Occasionally he had

puffy erythematous patches on his face and trunk, and once a big, swollen red and very tender patch on one gluteal region. Occasionally he had slight fever, and trypanosomes could usually be found in his blood. A principal complaint was of weakness and stiffness of the legs.

He was subjected to a variety of treatments, including arsenic and trypanroth, but not, so far as I know, atoxyl.

I lost sight of him. I heard that ultimately well marked sleeping sickness symptoms set in, and he died in University College Hospital in 1906.

VI.—Mrs. R., aged 31, had resided on the Congo (Bogandango) from 1898 to 1902, and, with the exception of fever for three days, during all that time had enjoyed good health. After furlough in England she returned to the Congo in September, 1903. She kept fairly well till June 15th, 1905, when she had a severe attack of abdominal pain, vomiting and diarrhoea. These symptoms recurred three days later (June 19th), when they were accompanied by fever and, on the following day, by haemoglobinuria. The haemoglobinuria persisted for five days. During convalescence she noticed that her right ankle had become enormously swollen, purplish in colour and very painful; at the same time a gland in the corresponding groin enlarged to the size of a hen's egg. Fever returned on June 26th and subsequently, off and on, about every four or five days, till September, when, being greatly debilitated, she was ordered home. On her way down river she was examined by Dr. Broden at Leopoldville, who found trypanosomes in her blood, besides enlarged cervical glands and a rapid pulse (120) with a normal temperature.

I saw Mrs. R. on October 9th, 1905. She was then very much emaciated, feeble and sallow. There were patches of ringed erythema on her chest and flanks and some enlarged cervical glands (right supra-clavicular). The spleen also was enlarged, and over the right ankle I found some reddish staining of skin, the remains of the inflammation in June. Trypanosomes were present in the blood; blood count 3,700,000.

She was sent to hospital and treated with arsenic and, later, Donovan's solution. On November 22nd she commenced atoxyl injections up to two grains twice a week. Over that dose the drug

seemed to cause nausea. Relatively the dose was a medium one, as she weighed only ninety pounds when treatment commenced.

On November 1st her right ankle became swollen and so painful she could not walk; but from the time atoxyl was commenced improvement set in and persisted. The erythema and the trypanosomes disappeared; temperature, which had been variable, became steady and normal, and her weight rapidly increased. Within a couple of months, from being sallow and emaciated she became ruddy and plump, and felt in excellent health.

After her discharge she returned from time to time to hospital to show herself and to have her blood examined. Trypanosomes were not found again; the erythema did not return; monkeys injected (January 12th, 1906) with her blood were not infected (March 29th, 1906), and good health continued. She left for the Congo on 8th March, 1907, against advice, but promising to continue the atoxyl injections.

I am informed that a letter, dated 11th September, 1907, had been received from her husband in which it is stated that 'she has been getting stronger and has been able to do quite a lot of language work. But she has to take great care, for evidently there is something causing a rise of temperature occasionally.' Soon after her arrival on the Congo she had a haemorrhage of some sort which pulled her down very much; apparently, she has taken some time to recover from this; possibly, judging by the temperature, the trypanosomes are again active.

VII.—H. C. C. S., aged 36, an engineer, arrived at Benguella, Portuguese West Africa, in June, 1904. His work took him up country some 100 to 150 miles from the coast. He had his first fever the following November. Attacks recurring very frequently, he had to be invalided, and arrived in England on May 29th, 1905. Soon after landing he had two attacks. I first saw him on June 23rd. He had no fever at the time, but he was anaemic and his spleen was enormously enlarged. I put him on quinine, 15 grains every tenth and eleventh day. Notwithstanding these doses fever kept recurring every few days. My *locum tenens* saw him on August 15th and ordered him five grains of quinine three times a day, apparently with benefit, for in a note dated August 24th it is stated that he had no fever, and that the spleen could no longer be felt. Subsequently

the patient married and returned to Benguella during the autumn of 1905.

For a time he kept fairly well and did much hard work in the interior on railway construction. He remembers that about this time he was bitten or stung on the leg by some unrecognised animal, supposed to be a centipede or scorpion. The part swelled and was very painful.

Fever now returned and, in addition, he got dysentery. Between the two he became so ill that he had once more to return to England, where he arrived on February 17th, 1906.

I saw him the same day. He was in bed. He had no fever at the time, but he was intensely anaemic, emaciated and weak, and evidently very ill. Both spleen and liver were much enlarged, the latter being tender as well. He was passing from four to five dysenteric stools daily. Quinine he said, aggravated the dysentery and gave him severe gastralgia. I examined his finger blood but found no malaria or other parasites in it. As he had not taken quinine recently, I was surprised at the absence of malaria parasites. I saw him daily, and on 22nd February, observing that the spleen had undergone a sudden increase in size, and from this suspecting an impending malarial attack, I gave orders that I should be sent for so soon as temperature rose. A few hours later I was summoned. The temperature was then 103°. I took blood films and found in them, not malaria parasites, as I expected, but considerable numbers of trypanosomes. I now made a careful examination of the skin and lymphatics, and recognised several characteristic patches of erythema and at least one definitely enlarged posterior cervical gland. Temperature rose on this occasion to 106° but quickly fell, although for three or four days some fever of a remittent type persisted. Trypanosomes were found for some days, their numbers gradually becoming fewer under the atoxyl treatment which was at once instituted.

From time to time, at intervals of a few weeks, although the general condition of the patient, including the dysentery, steadily improved, there were short recurrences of fever, each recurrence being associated either with the appearance of trypanosomes, or of benign tertian malaria parasites in the blood; so that without the microscope it was impossible to say whether a given relapse was trypanosomal

or malarial in nature. On the discovery of the malarial infection quinine was given systematically at definite intervals as well as atoxyl, and was now very well borne.

At first the atoxyl was given in one grain doses (10 per cent. solution) hypodermically every third day. It was gradually raised to 2·3 grains, beyond which, after not a few attempts, it was impossible to push it. Every time a 2·5 grain dose was given, violent and alarming gastralgia ensued. The 2·3 grain doses of atoxyl, and occasional 10 grain doses of quinine were therefore steadily persisted with.

Under the persevering use of these drugs and with careful nursing the patient slowly improved, the erythema, the adenitis and the dysentery disappearing. When the weather became milder, and he could walk about, the patient was removed to a healthy and bracing place in the country, where I saw him from time to time. There the febrile attacks became milder, returning at longer intervals, the trypanosomes being found only occasionally in the blood and never in large numbers. In the course of the summer of 1906 he suffered at one time from severe dental neuralgia, and twice from smart attacks of orchitis. Notwithstanding this, general improvement continued. He spent the winter of 1906-7 on the high Alps, where, with the exception of a brief but painful attack of what might have been erythema nodosum in one leg, he kept quite well and gained strength. I saw him again on July 25th, 1907, and noted that 'he had had no fever since 21st February with the exception of that attending a slight cold in May (temperature 101°). Weight $9\frac{1}{2}$ stone—the highest he has ever been in his life. Feels quite well.'

He refused to consider himself any longer an invalid. A situation was offered to him in South America, my consent being a condition of the appointment. This I promised provided injection of his blood into monkey, rat and guinea-pig proved negative. These injections were made in August. All the animals were alive and free from trypanosomes in October when he sailed for South America in the best of health, promising to keep up the atoxyl injections for another year and to report progress.

A letter just received and dated 31st December, 1907, stated that 'he is very well indeed,' and 'to see him now no one would think he had ever had an illness.'

VIII.—C. G., aged 34, an engineer, was stationed at Katanga on the Upper Congo (Lualaba river) for three and a half years. He took five grains of quinine daily and enjoyed excellent health till November, 1906. About that date he began to suffer from fever, apparently uncontrolled by quinine. On November 9th, his temperature at the time being 102°, he started to return to England viâ Rhodesia and the Cape, riding 500 miles of the way on a bicycle and suffering from fever all the way. On the voyage from the Cape he gave up taking quinine as it seemed to do him no good. Fever persisting, he became bilious and yellow.

I saw him on his arrival (January 5th, 1907). His temperature was 103°, pulse 112. He was somewhat emaciated, slightly icteric and markedly anaemic. Liver and spleen, especially the latter, were both enlarged. The superficial cervical glands were also slightly enlarged and the skin of the trunk was splashed with rings and patches of erythema multiforme. A blood examination gave 2,848,000 erythrocytes per c.mm. and 4,000 leucocytes per c.mm., the large mononuclears being in marked excess (37·3 per cent). Malaria parasites were not found at that time, but trypanosomes were numerous.

Atoxyl.—He was at once put to bed and atoxyl in hypodermic injections begun. At first the injections were given every second day, the dose being rapidly increased from $1\frac{1}{2}$ to 7 grains, and occasionally 8 grains. In a few days trypanosomes had disappeared from the peripheral circulation, so that when Dr. Todd, of Liverpool, saw the patient with me on January 11th he failed to find a single specimen during a prolonged examination. The skin eruption, the adenitis, the fever and, in great measure, the debility disappeared equally rapidly. On January 13th and 14th there was a return of fever which, on microscopical examination, proved to be malarial—benign tertian. Quinine was now given in addition to the atoxyl and repeated at intervals ever since.

Except during four short periods the atoxyl injections have been continued. They were intermitted from May 26th to June 12th, from June 26th to July 9th, and from July 16th to July 25th, when he was taking perchloride of mercury; and also from November 6th to November 27th (three weeks), when he was being treated with sodio-tartrate of antimony. The dose of atoxyl varied from $2\frac{1}{2}$ to

9 grains; latterly it has been 3 grains every second day. At no time has there been any local reaction or sign of arsenical poisoning.

Perchloride of mercury.—Notwithstanding several febrile attacks and frequent and careful examination of the blood, no trypanosomes appeared in the peripheral blood till May 21st. On that day a few were found. Atoxyl in 8-grain doses was being administered at the time. The same dose was repeated on the 22nd, 24th, 26th and 28th. The trypanosomes having disappeared, hypodermics of perchloride of mercury in $\frac{1}{2}$ per cent. solution were commenced and repeated daily for fourteen days, the dose being rapidly increased from 15 to 30 minims (about one-seventh of a grain), at which it was kept for five days, when atoxyl was resumed in $2\frac{1}{2}$-grain doses every second day. A week later there was another febrile attack concurrent with a fresh invasion of trypanosomes. The dose of atoxyl was now increased to five grains. After four injections of this strength, and the trypanosomes having disappeared, the perchloride was resumed from June 27th to July 6th. On July 10th there was a rise of temperature to 101·6°, but trypanosomes were not found, though carefully searched for; the atoxyl was again resumed. The perchloride injections having caused much pain and irritation, Hydrarg. c. creta, one grain three times a day, was substituted and continued from the 15th to the 22nd of July, when, the gums being slightly tender, it was stopped and the atoxyl resumed. On August 11th temperature rose to 101·7°, and trypanosomes once more appeared in the blood.

Parafuchsin.—Treatment with parafuchsin (kindly suggested and supplied by Professor Ehrlich) was begun on August 16th, atoxyl in $2\frac{1}{2}$, $3\frac{1}{2}$ and occasionally in 8-grain doses every second day being continued at the same time. Beginning with 5 grains, the dose of parafuchsin was gradually raised by 5 grains at a time till 20 grains were taken three times a day by the mouth in cachet. These large doses, though continued till October 13th (nearly two months), caused no disturbance. There was no intestinal irritation, nor, although the urine and sweat were coloured by the drug, was there albuminuria or urinary irritation. Trypanosomes, which were present when the parafuchsin was commenced, persisted till August 29th—a fortnight. After this, though looked for almost daily, they disappeared for a time.

The last dose of parafuchsin was taken on October 17th. Ten days later there was a rise of temperature, and once more the parasites appeared. About this time the patient apparently got a chill while salmon fishing and there was some rise of temperature, which was repeated on November 1st and 2nd, when a very large influx of trypanosomes was noted.

Sodio-tartrate of antimony.—On November 8th I administered a hypodermic injection of sodio-tartrate of antimony (kindly supplied by Mr. Plimmer)—$\frac{1}{2}$ a grain, and followed it up with injections of 1, $1\frac{1}{2}$, 2, and 2 grains on the 10th, 11th, 12th and 15th respectively. There was no nausea, intestinal disturbance, or albuminuria following the injections, but the local pain and irritation were great. The parts became puffy, then hard, then fluctuating. One swelling, which had become very tense and discoloured, and seemed as if about to rupture, I incised. About an ounce of dark sanious fluid escaped, and after a week an ash-grey slough was seen at the bottom of the wound. The slough took a fortnight to come away, and the wound, which never suppurated, took a very long time to heal. The other swellings took several weeks to subside. The pain consequent on the injections was very great, demanding morphia. It would subside towards morning and be comparatively in abeyance during the forenoon, but each afternoon it would wake up again, being most severe during the night, rendering sleep impossible. There was very little rise of temperature. The pain consequent on an injection lasted about a fortnight.

It was remarked both in this and in another case that although given in different strengths ($\frac{1}{2}$ to 1 per cent.) the weaker solution of antimony was quite as painful as the stronger; and, also, that intramuscular injection, though equally painful at first, caused less swelling than subcutaneous injection.

When it became evident that hypodermic injection of antimony was impracticable, the drug was given by mouth to the extent of two grains a day diluted in two or three pints of water. This, along with three grain doses of atoxyl, is being continued. It causes no nausea or irritation of any sort.

Up to the date of this note there has been no return of fever. The patient is leading an active country life and is feeling perfectly well.

IX.—W. R. E., aged 46, was in the West Indies from 1881 to 1903, exploring and planting.

In 1903 he went to Northern Nigeria as a Forestry Officer. Although his duties took him all over the country and exposed him to much hardship, he enjoyed excellent health during his first tour of twenty months. After furlough in England he returned to Northern Nigeria in October, 1905, and kept perfectly well till 24th September, 1906. About the latter date he got an irregular fever which resisted quinine in full doses. Not improving he was invalided, and arrived in England on 29th November, 1906. He had slight fever on the voyage home, and at that time observed certain red patches on his skin, which he attributed to pressure from his clothes. After six weeks in the country, during which he took long walks and, with the exception of a slight fever at Christmas time, felt very well, he was sent to me officially for report.

I saw him first on January 15th, 1907. On examination I found his trunk covered with rings and patches of erythema; several cervical, axillary and inguinal glands were enlarged though painless; spleen and liver were also slightly enlarged and his pulse was quick—100. I found trypanosomes in his blood. There were no other symptoms of trypanosomiasis or of other disease. He said he felt fairly well. I sent him to hospital for treatment and observation.

Atoxyl injections were begun on January 25th, 1907. They were given every second day, the dose being gradually raised to seven grains. He remained in hospital from January 21st till March 4th, 1907. For the first fortnight temperature was somewhat erratic, ranging from 98° to 99° F.; once it was 100·8°. Subsequently, with the exception of one short rise of a few hours to 101·8° on March 5th, and attributed to a cold, temperature was steadily normal or subnormal. Erythema and trypanosomes disappeared about February 12th.

After leaving hospital he returned to his home in the country, where the injections were continued. About July symptoms of peripheral neuritis—not of a very pronounced character—showed themselves. He was again taken into hospital and a course of mercury substituted for the atoxyl. The gums were slightly 'touched.' The neuritis subsiding, the atoxyl was resumed in smaller doses. He now became so well that he wished to return to

Africa. The atoxyl was stopped for a fortnight with a view to testing his supposed cure by injection of his blood into animals. At the end of the fortnight trypanosomes were again found in the blood and the atoxyl resumed. I saw this patient lately (16th January, 1908). He says he never felt better in his life; he looks quite well, and no indication of trypanosomiasis can be detected on careful examination.

X.—A. P. P., an engineer, aged 35, arrived at Boma, Congo River, on June 22nd, 1907. He was then in perfect health, and proceeded at once up country to a point about 150 miles above Stanley Pool, where he and his companions camped on the river bank from June 28th till July 17th. Four days after his arrival there he began to ail with anorexia, depression, languor, drowsiness, and on 12th July took to bed with fever (102°). On July 17th his temperature had reached 107°. Next day he was brought to Leopoldville (104°), and on the following day—19th July—Dr. Broden found trypanosomes in his blood. He received a large dose (I understood 1·5 gramme) of atoxyl hypodermically on the 20th. This gave rise to violent gastralgia, but on the 21st temperature had become normal and has remained so ever since, with the exception of slight brief rises (99·5 to 102·4°) which recur with some regularity every fortnight or three weeks. On 23rd July daily injections of ·25 gramme of atoxyl were commenced and, with occasional intermissions of a day or two and increases of the dose to ·5 gramme, were continued till his arrival in Liverpool about the middle of October.

Trypanosomes were unusually persistent in the peripheral blood in this case. Dr. Broden found them when the patient was at Leopoldville every time he looked for them. Dr. Breinl, who examined him on his arrival in Liverpool, found them, notwithstanding intensive doses of atoxyl, on each of five successive days; and I found them whenever I examined the blood—that is, on every alternate day—between October 23rd and November 8th.

When I saw the patient for the first time on October 23rd he informed me that he had had no cutaneous eruption, and that only once—during the initial fever—when one slightly enlarged gland was detected on the right side of the neck—any adenitis. An inflamed patch of skin on the dorsum of the right foot, which began on the 20th of September, and which he attributed to prickly heat, had

almost disappeared when I saw him. The spleen was slightly enlarged, and he looked more anaemic than the blood count (4,000,000) indicated. Appetite was poor, and he felt weak and depressed. There was no palpitation or breathlessness, and no headache even when he had fever. The only pain he remembered was intense aching in the legs coming on every night and keeping him from sleeping; this disappeared when he left Leopoldville and has not recurred.

On November the 8th, trypanosomes being present in small numbers in his blood and temperature being normal, for the first time during his illness the characteristic erythema showed itself on the skin of the trunk. At the same time and for a day or two previously he had been profoundly melancholic, so much so that I feared the nervous system was becoming implicated and that the terminal phase of the infection was about to set in. He was so depressed I was afraid to allow him to go out alone.

On the day the erythema appeared (8th November) I gave him a hypodermic injection of half a grain of sodio-tartrate of antimony, and also on the following days 1, 1½, 2, and 2 grains respectively, and again after two days another 2 grains. The apparent effect of these injections was remarkable. By the third day the erythema had disappeared, his spirits had become good, and for the first time trypanosomes could not be found in the blood. This hopeful condition persisted till November 26th, when depression, though not so intense as on the former occasion, returned and trypanosomes in greater number than I recollect to have seen them in human blood were once more found. On November 26th and 27th he had two grains of antimony by the mouth. I was afraid to resume the antimony hypodermics on account of the intense irritation and pain they gave rise to. Given by the mouth the drug caused nausea and seemed to increase the depression. It was stopped, therefore, and atoxyl resumed. By the 30th trypanosomes had again disappeared and the patient was feeling much better. He left for New York on December 12th, with instructions to continue the atoxyl. A letter just received states that he is feeling much better.

The more important facts (especially as bearing on treatment) of these ten cases are summarised in the following table:—

Case.	Where acquired.	Duration.	Treatment.	Present state.
1	Congo	7 years	Arsenic (*Liquor arsenicalis*)	Well
2	Gambia	1 year 8 months	Arsenic, quinine, urotropine	Dead
3	Congo	2 years 3 months	Arsenic, quinine, methylene blue, etc.	Dead
4	Uganda	3 years	Arsenic, trypanroth, atoxyl	Apparently well
5	Uganda	4 years	Trypanroth-arsenic	Dead
6	Congo	2 years 6 months	Atoxyl	Apparently well
7	Benguela	2 years 3 months	Atoxyl	Apparently well
8	Lualaba River (Congo)	1 year 3 months	Atoxyl, parafuchsin, perchloride of mercury, antimony	Apparently well
9	Northern Nigeria	1 year 4 months	Atoxyl, perchloride of mercury	Apparently well
10	Congo	6 months	Atoxyl, antimony	Improved

Any conclusions we may be tempted to draw from these and other recorded cases as to the effect of treatment in human trypanosomiasis must be tempered by the consideration that we do not as yet know the limit of the duration of the infection in man, that it certainly may run a course of three or four years, and that the lower animals, especially the smaller laboratory kinds, as regards their reaction to drugs, form no very reliable guide to the action of the same drugs in man.

Subject to these considerations we may provisionally infer that:

1. Trypanosomiasis in man is not necessarily a fatal disease.

2. Atoxyl has a marked effect in checking the clinical manifestations of the infection and in causing the parasites to disappear from the peripheral circulation.

3. Notwithstanding continuation of atoxyl treatment, parasites may reappear again and again at uncertain intervals, and usually concurrently with a rise in temperature.

4. Nevertheless, if the drug be persevered with, the parasites ultimately disappear for good and do not return.

5. Large doses of atoxyl are not necessary to secure this result.

6. Large doses of atoxyl should be avoided, as they are apt to cause serious lesions, peripheral neuritis, optic atrophy, gastro-intestinal inflammation, and other toxic conditions which necessitate suspension of a valuable remedy.

7. Trypanroth, mercury and parafuchsin seem ineffective in human trypanosomiasis.

8. Antimony may have a therapeutic influence in trypanosomiasis, but the hypodermic injection of the sodio-tartrate is impracticable.

The prospects of atoxyl treatment I consider most hopeful. As regards efficiency, promptness and mode of action, it seems to me that it is almost on a par with mercury in syphilis and quinine in malaria; and I think in using atoxyl we should conform our practice to what experience has taught us to be the best methods of using these other efficient and long tried remedies.

I do not believe we can kill the trypanosome outright by one or two large doses of atoxyl, any more than we can kill the treponema of syphilis or the parasites of malaria by large doses of their respective specifics. Mercury does not immediately cure syphilis, nor does quinine immediately cure malaria; but they deprive the respective parasites of their pathogenic qualities and keep the patient alive and in good health till, in process of time, the parasites either die out or become permanently inert. So I read the action of atoxyl in trypanosomiasis, and so I would regulate its administration, being careful, as we would with mercury or quinine, not to push the drug too far, and thereby necessitate its suspension. Case 7 distinctly shows that a dose of 2·3 grains given twice a week controlled the disease; why then risk poisoning by a larger dose? Some of my patients have been for months on 2 to 4 grain doses two or three times a week and have done well.

I would therefore suggest for the routine treatment of trypanosomiasis, a two to three grain dose of atoxyl every second or third day and kept up for at least two years. At the same time concurrent specific disease such as malaria, syphilis, &c., should be carefully treated; and, further, the patient should be brought home to his native country, be spared fatigue, worry, exposure, excesses of all

kinds and be placed in the most favourable hygienic conditions possible.

I fear to overstate my opinion of the value of atoxyl given in this way in the treatment of trypanosomiasis. I am fully conscious that the evidence in its favour, though strong, is far from complete. However, besides direct evidence derived from its actual use in the disease itself, there is a good deal of collateral and indirect evidence derivable from its employment in other protozoal diseases—syphilis for example. Recently I had an experience of this kind which has greatly impressed me. The case was one of Kala-azar—admittedly an almost invariably fatal disease. The patient had been ill for many months. He had the usual hectic type of fever, was miserably emaciated, and had enormously enlarged spleen and liver; the spleen extended beyond the umbilicus. Liver puncture yielded the Leishman body in profusion, so that there could be no question as to diagnosis. He was given atoxyl injections over a long period, at first apparently with little benefit. Severe inflammation of gums, cheeks and palate, together with symptoms of peripheral neuritis setting in, the injections were stopped. Shortly afterwards the patient left hospital, in my opinion then, apparently to die. Soon after leaving hospital symptoms began to subside; he lost fever and sweats; he gained strength and appetite; his spleen and liver shrank, and, when I saw him a week ago, he had been free from fever for five months and appeared to be quite well, although still a little weak. The liver was almost normal in size, and the spleen could just be felt under the ribs. Was this atoxyl? If so, there is hope now for the victims of yet another formerly hopeless disease.

Before concluding this paper, there are one or two points I would like to draw attention to.

It is not a little remarkable that of the ten cases of trypanosomiasis in Europeans which have come under my personal observation three of them were females. Considering the very small number of European females and relatively large number of European males in tropical Africa, this large number of females attacked with trypanosomiasis is a striking circumstance. I am dealing, it is true, with very small numbers, and it is quite possible that the relative disproportion I remark on is accidental; but when we reflect that whereas women in Africa expose themselves, as

compared to men, comparatively little to the conditions favouring the attack of *Glossina palpalis*, the disproportion becomes still more striking.

Another point that has attracted my attention in connection with these cases is the frequency (four in the eight cases in which the point was inquired into) with which the symptoms were immediately ante-dated by what was described as a bite on the leg. The biting animal may have been a Glossina, but in the case of females—and two of the bitten ones were females—one would suppose that the petticoat would afford a protection even more effective than the trouser does in men.

Too much weight must not be attached to what may have been mere coincidence; but these facts are curious, and suggest further inquiry as to the possibility of some blood sucker, perhaps some species of house vermin, being an occasional vector of *Trypanosoma gambiense*.